Asthma: 1. Pathophysiologic features and evaluation of severity

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The response of asthmatic airways to irritant stimuli is twofold: bronchoconstriction and airway inflammation. The inevitable mechanical consequence of bronchoconstriction is hyperinflation of the lungs, a phenomenon that produces characteristic clinical and radiologic signs. Hyperinflation helps to maintain airway patency at the expense of increased respiratory muscle work. Airway inflammation accounts in large part for the increased ventilatory drive of asthmatic patients, which results in alveolar hyperventilation and dyspnea. The resultant respiratory alkalosis further compromises tissue oxygen delivery both by cerebral vasoconstriction and by the leftward shift of the oxyhemoglobin dissociation curve. Optimal correction of hypoxia in the hyperventilating asthmatic patient requires delivery of oxygen at a high flow rate. Failure of patients with asthma to respond to simple bronchodilator therapy indicates the presence of continuing inflammatory activity and hence the need for anti-inflammatory therapy and frequent monitoring.

Les bronches de l'asthmatique réagissent de deux façons aux irritants: par la constriction et par l'inflammation. De la première résulte inévitablement l'hyperaération des poumons avec ses manifestations cliniques et radiologiques typiques. Cette hyperaération sert à assurer la perméabilité des voies aériennes au prix d'une augmentation du travail musculaire de la respiration. Quant à l'inflammation, elle explique pour une large part le besoin que ressent l'asthmatique de respirer plus; il en résulte hyperventilation alvéolaire, dyspnée et alcalose gazeuse. Cette dernière, par le biais d'une vasoconstriction cérébrale et d'une déviation vers la gauche de la courbe de dissociation de l'oxyhémoglobine, compromet encore plus l'apport d'oxygène aux tissus. Afin de corriger au mieux cette hypoxie de l'asthmatique en hyperventilation, il faut une oxygénothérapie à haut débit. Chez le malade qui ne répond pas au seul traitement bronchodilatateur, on doit penser à la présence d'une inflammation persistante nécessitant une thérapeutique anti-inflammatoire sous proche surveillance.

Although there is no universally accepted definition of asthma, clinicians are comfortable to make this diagnosis and even to categorize asthma as intrinsic, extrinsic, occupationally induced, exercise-induced and drug-induced.[1] The pathophysiologic feature common to these diverse clinical presentations is airway hyperreactivity. Regardless of whether the provoking agent is an allergen, a chemical agent, cold air, exercise or another stimulus, the response of hyperreactive airways is twofold: bronchoconstriction and airway inflammation. While therapeutic efforts are directed to the relief of bronchoconstriction, the importance of airway inflammation is commonly underestimated in the evaluation and management of asthma.

In the regrettably large number of autopsy specimens that have become available, asthmatic airways show shedding or loss of epithelium, accumulation of inflammatory cells, widespread mucus plugging, submucosal edema and smooth muscle hyperplasia.[2-4] Although asthma may be viewed clinically as intermittent ("mild") or chronic ("severe"), there is considerable overlap of these scenarios within and among patients, with no evidence to suggest that the pathological features differ qualitatively from one type of asthma to another.

The severity of asthma is generally equated with the severity of airflow obstruction. However, the terms are not synonymous. Since asthma is a treatable condition, it should be possible to achieve nearly normal pulmonary mechanics in most, if not all, patients with asthma. Thus, when adequately treated, a patient with severe asthma may have only mild airflow obstruction; in this setting, the

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severity of asthma would be better gauged by the amount of medication needed for control. Asthma may also be regarded as severe in a patient who has minimal airflow obstruction most of the time but who suddenly experiences asthma of life-threatening severity with minimal provocation. Such labile asthmatic patients may be identified by a marked sensitivity to inhaled methacholine, as measured in the pulmonary function laboratory,[5] or by the presence of an exaggerated circadian rhythm of the peak expiratory flow rates.[6]

Pathological changes in asthma are likely generated by the release of mediators from the abundant mast cells of the bronchial lumen and submucosa and by the neutrophils and eosinophils that are attracted by chemotaxis.[7-9] Released chemical mediators have bronchoconstrictor properties and are known to include histamine, serotonin, leukotrienes, prostaglandins and platelet-activating factor. Mucosal changes are mediated by oxygen radicals, peroxide and proteolytic enzymes. Extensive research efforts are being directed at a more detailed characterization of this chemical cauldron. However, the practising clinician needs to know the practical implications of the newer concept that asthma is an inflammatory disorder rather than merely a bronchospastic one. Hence, in this review we address the clinicophysiologic consequences of airway inflammation, the potentially disastrous result of failure to make frequent reassessments, and the practical aspects of gauging disease severity. In the next issue of *CMAJ* we will discuss therapeutic aspects, with particular emphasis on newer modalities of therapy and the treatment of patients whose asthma is resistant to conventional therapy.

Clinicophysiologic consequences of airway inflammation

Asthmatic airways may be narrowed by bronchial smooth muscle spasm, mucosal inflammation and occlusion of the lumen by tenacious secretions. The relative contributions of these mechanisms to airway obstruction change with time, such that mucosal inflammation and inspissation of secretions assume greater importance as the asthmatic attack continues. When an asthmatic patient is challenged with the appropriate immunologic, chemical or physical trigger, the initial, relatively short-lived response occurs in the large airways and is readily detected with conventional pulmonary function tests.[10,11] After these proximal airway changes, the smaller, peripheral airways may become constricted if the stimulus has been severe or is continuing or if the airway reactivity is marked. This peripheral constriction is slower in onset but of greater duration than the constriction of the large, central airways. Peripheral airway constriction is more difficult to detect either clinically or with conventional pulmonary function testing and is more resistant to simple bronchodilator therapy. Thus, asthmatic patients with any significant degree of airway inflammation report short-lived or submaximal relief with their usual inhaled bronchodilator. As the more sensitive tests required for detecting peripheral airway changes are not available to most practising physicians because of cost and complexity, bedside and office evaluation is difficult unless attention is directed toward an inevitable consequence of small-airway narrowing: hyperinflation of the lungs.

As a result of airway narrowing and reduced expiratory flow rates, expiration is interrupted by early airway closure. The resultant trapping of gas increases the lung volume. This hyperinflation can readily be detected and quantified in laboratories equipped to measure residual volume and functional residual capacity and can be shown to decline progressively during drug-induced recovery from an acute attack.[12,13] On the one hand, hyperinflation is of value to the patient: operating at a high lung volume helps maintain airway patency and increases the elastic recoil of the lungs. On the other hand, breathing at high lung volumes requires marked increases in respiratory muscle work, which increases the patient's sensation of dyspnea.[14,15] The increase in muscular work also provides the clinician with important clues that hyperinflation has occurred and that extensive small-airway narrowing must be present.

Hyperinflation is characterized by decreased cardiac dullness to percussion and descent of the zone of hepatic dullness.[16] Radiologically there is flattening of the diaphragm and increased retrosternal lucency.[17] Attempts to generate high negative intrapleural pressures are reflected in the obvious use of accessory muscles of inspiration (sternocleidomastoid contraction) and by intercostal indrawing.[18] The normal expansion of the upper abdomen produced by inspiratory descent of the diaphragm may be absent. The combination of accentuated positive intrapleural pressure during expiration and negative intrapleural pressure during inspiration magnifies the physiologic swings in systolic blood pressure that accompany respiration.[19] Pulsus paradoxus is the result, with the systolic pressure dropping by more than 12 mm Hg during inspiration. Significant pulsus paradoxus first appears when the forced expiratory volume in 1 second (FEV_1) has fallen to below 50% of the control value, the degree of pulsus paradoxus correlating approximately with the decrease in FEV_1.[10] Even electrocardiographic changes may point to the presence of hyperinflation, with p-pulmonale resulting from the high negative pleural pressures and increased right ventricular transmural pressures in severe asthma.[12,20]

When hyperinflation is severe enough and persists long enough, the respiratory muscles may fatigue. In asthma, fatigue is likely accelerated by hypercapnia (if present), hypoxemia and reduced blood flow in muscles that are working at a mechanical disadvantage when shortened to below their optimal length by thoracic overinflation.[21-23]

Physical signs of respiratory muscle fatigue are easily elicited: the respiratory rate increases, alternation between abdominal and rib cage breathing (respiratory alternans) occurs, and paradoxical diaphragmatic movement can be detected by palpation over the upper part of the abdomen.[24] These physical signs may precede the development of overt respiratory failure and give warning of impending respiratory arrest.

Aside from hyperinflation, another important consequence of airway inflammation in asthma is modification of ventilatory drive. In asthma a low partial pressure of carbon dioxide (P_{CO_2}) is far more common than a high P_{CO_2}, even in the presence of severe airways obstruction.[12,25] Most episodes of asthma are characterized by alveolar hyperventilation and intense dyspnea; hypoventilation along with hypercapnia occurs so rarely that it is regarded by the clinician as a grave prognostic sign. On clinical grounds alone it is clear that ventilatory drive is increased in asthmatic attacks. The increased ventilatory drive arises primarily from increased afferent activity from the respiratory muscles in their struggle against the mechanical load and from pulmonary irritant receptors of the vagus nerve. The respiratory alkalosis produced by this increased drive to breathe has several deleterious effects. Cerebral oxygen delivery is compromised both because of the cerebrovascular constriction that hypocapnia causes and because tissue oxygen delivery is inhibited by the leftward shift of the oxyhemoglobin dissociation curve.[26] The latter phenomenon, by increasing hemoglobin's affinity for oxygen, creates a paradoxical situation in which blood oxygenation is maximized while release of oxygen from blood into the tissues is minimized. The patient thus presents without cyanosis and with falsely reassuring blood-gas levels in the presence of potentially damaging tissue hypoxia.

Because the clinical manifestations of tissue hypoxia are late and unreliable indicators of the severity of an asthma attack, supplemental oxygen administration and periodic monitoring of the arterial oxygen tension are mandatory in all acutely ill asthmatic patients. Oxygen therapy is best delivered with a high-flow-rate system. The tachypneic patient generates inspiratory flow rates that easily exceed the flow rates of most oxygen delivery systems. As the patient-generated flow rate climbs above the physician-prescribed flow rate, room air is entrained into the mask or around the nasal prongs, diluting the inspired supplemental oxygen.[27] The choice of oxygen delivery system is less important than the flow rate at which the oxygen is given.

Importance of frequent reassessment

It is now general knowledge that asthma can be fatal and that in some countries with a sophisticated level of medical care the death rates appear to have been increasing.[28] Yet as recently as 1983 an editorialist in the *Lancet* found it necessary to point out that some physicians still considered the disease "a benign nuisance related mainly to emotional problems".[29] Osler's view that asthma is a nonlethal disease and that asthmatics pant into old age was standard teaching until the late 1960s.[30] At that time an epidemic of sudden and unexpected deaths from asthma erupted in the United Kingdom, Australia and Norway and was blamed on excessive use of the newly introduced adrenergic bronchodilator aerosols. However, when Read[31] analysed the level of care the patients had received during their final illnesses, he found that their deaths were neither sudden nor, in retrospect, unexpected. Speizer and colleagues,[32] in a similar analysis, found that most of the patients who died from asthma had not received corticosteroids. In their analysis of hospital deaths from asthma Ormerod and Stableforth[33] found that 87% of patients had had prior admissions for asthma, 60% had received intravenously administered aminophylline and 47% had had central cyanosis. But over the first 24 hours in hospital the proportion of patients in whom repeat testing of arterial blood-gas levels was performed was 0%, the proportion in whom serial flow measurements were made was 0%, and, although 27% required assisted ventilation, not one patient was found to have received an aerosol bronchodilator.

Failure to monitor asthmatic patients adequately is a problem not limited to the hospital. Ambulatory patients with asthma frequently suffer from the same not-so-benign neglect as their hospitalized counterparts and suffer similar consequences. Rea and associates,[34] in a case–control study of deaths from asthma, showed that pulmonary function testing was often neglected for up to a year before death and that this failure to monitor pulmonary function was a major independent risk factor for a fatal outcome.

From the many studies on fatal asthma that have been published, it has become clear that few asthmatic patients die when their therapy is adequate and when they are educated about their disease and its management.[28] For these educational exercises to be effective, physicians must guard against forcing their prejudices on their patients. Morris,[35] for example, found that most physicians believed that dyspnea in asthma was only expiratory — that breathing in was easy but breathing out was difficult. His survey of patients with asthma and our study of expiratory loading[36] showed that this preconception was wrong. What matters to the patients is their inspiratory distress, which is readily explained on the principles of load perception and the increased drive to their inspiratory muscles from lung irritant receptors.

The performance of pulmonary function tests offers an opportunity for the physician to nurture a sense of trust and confidence in the management plan. The patient can be asked to correlate subjective symptoms with objective measurements such

as peak expiratory flow rate, tabulated in a diary format designed to include relevant day-to-day events (e.g., unusual foods, respiratory infections and travel).[37] Most patients respond positively to disclosure and explanation of the results of their laboratory tests and definition of therapeutic goals. The demonstration of rapid response to bronchodilators can be used to encourage fastidious use of aerosol medications. Poor responsiveness to these agents can be used to explain why a more aggressive therapeutic approach, such as the use of inhaled steroids, is needed.

Evaluation of asthma severity

Asthma is a disease in which life-threatening deterioration may occur suddenly. If such episodes are to be treated promptly and attention is to be paid to their prevention, the patient must share the responsibility for continuing assessment. Constant communication between patient and physician should result in early institution of effective therapy at the first indication of relapse. The patient can assess airflow obstruction using a simple peak flow meter, with the understanding that the physician must be contacted if values fall below some previously agreed-on level, such as 200 L/min.

At office and emergency department visits, again, simple techniques such as peak flow measurements before and after bronchodilator inhalation can be invaluable in following progress. Automated digital spirometers should be available on hospital wards, with the attending staff using them both regularly and whenever the patient's apparent recovery is interrupted by an exacerbation of dyspnea. A peak flow measurement of less than 150 L/min or an FEV_1 recording of less than 1 L should be regarded as indicative of asthma whose severity justifies oxygen and corticosteroid therapy. The same can be said of pulsus paradoxus, evidence of tissue hypoxia, a rising or elevated P_{CO_2} and respiratory muscle fatigue.

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